Revisiting interactions between hypoxaemia and $\beta_2$ agonists in asthma

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The excessive use of $\beta_2$ agonists has been associated with increased asthma mortality, although this seems to be due to confounding by disease severity rather than direct drug toxicity.\(^{1,2}\) Dose-response studies in stable asthmatics have shown the potential for high doses of salbutamol to produce direct or indirect cardiovascular sequelae mediated by extrapulmonary $\beta_2$ adrenoceptor stimulation including chronotropic and inotropic activity, peripheral vasodilatation, electrocardiographic changes, as well as hypokalaemia and hypomagnesaemia.\(^{3,4}\)

The potential for cardiovascular toxicity with high doses of inhaled $\beta_2$ agonists may be considered in the context of “the seed and the soil”. In terms of the “seed”, there are conflicting reports as to whether a full agonist such as fenoterol produces greater dose related systemic $\beta_2$ mediated systemic effects than a partial agonist such as salbutamol in asthmatic patients when comparing microgram equivalent doses with the same bronchodilator potency.\(^{4,5}\) In terms of the “soil” for salbutamol mediated adverse effects, concomitant diuretic therapy may augment hypokalaemic and electrocardiographic sequelae, concomitant corticosteroid may sensitize cardiac $\beta_2$ adrenoceptors, while the elderly exhibit increased chronotropy and peripheral vasodilatation.\(^{6,7}\) Patients with more severe asthma have reduced systemic effects of salbutamol due to reduced lung absorption so they may, in effect, be protecting themselves from adverse effects.\(^{8}\) The lung absorption of salbutamol may also be greatly influenced by the efficiency of deposition from different inhaler devices for the same nominal dose.\(^{9}\)

In acute severe asthma there may be adverse cardiovascular sequelae due to the presence of hypoxaemia and/or hypercapnia. Acute hypoxaemia on its own in healthy humans produces an increase in heart rate, a fall in systemic vascular resistance, an increase in cardiac output and pulmonary artery pressure, and impaired left and right ventricular relaxation without affecting left ventricular systolic contractility.\(^{10,11}\) Acute hypoxaemia also causes myocardial repolarisation abnormalities as evidenced by an increase in the heart rate corrected QTc interval and QTc dispersion.\(^{12,13}\) Acute hypercapnia on its own has no effects on left ventricular contractility or relaxation but causes systemic and pulmonary pressor effects as well as increasing QTc interval and dispersion.\(^{14,15}\)

The potential for an interaction between hypoxaemia and inhaled $\beta_2$ agonists is clinically relevant. In this issue of Thorax Burggraaf and colleagues from Leiden University have reported on eight mild asthmatics who were rendered hypoxaemic ($\text{SpO}_2 82\%$) for 60 minutes and given an 800 $\mu$g bolus of inhaled salbutamol via spacer after 30 minutes.\(^{16}\) The main positive findings from the study were that the combination of salbutamol and hypoxaemia resulted in significantly greater increases in heart rate and peripheral vasodilatation than hypoxaemia alone, amounting to a 32\% difference in forearm blood flow. At the same time, there were no significant differences in mean arterial pressure, QTc, or potassium responses. The combination of hypoxaemia with salbutamol resulted in a 30\% decrease in peripheral vascular resistance (mean arterial pressure divided by forearm blood flow), although it was noticeable that baseline values for peripheral vascular resistance with the combination started at 24\% and 18\% higher, respectively, than with salbutamol or hypoxaemia alone. Given that these were patients with mild asthma, and since severe asthmatics show a 41\% reduction in salbutamol bioavailability,\(^{17}\) extrapolation to severe asthmatics would approximate to an 18\% decrease in peripheral vascular resistance in response to an 800 $\mu$g dose of salbutamol via a spacer in combination with hypoxaemia. To put this into context, the equivalent nominal dose of salbutamol via a nebuliser would be 4100 $\mu$g.\(^{18}\)

Cardiovascular responses to acute hypoxaemia and inhaled $\beta_2$ agonists in healthy volunteers exhibit additive rather than synergistic effects.\(^{19,20}\) In particular, both hypoxaemia and inhaled $\beta_2$ agonists are responsible for causing abnormal myocardial repolarisation in terms of increased QTc dispersion, the latter being a sensitive surrogate for genesis of life threatening cardiac arrhythmias in susceptible individuals.\(^{21}\) However, in dogs rendered severely hypoxicemia in conjunction with high doses of isoprenaline, death occurred from a fall in cardiac output rather than from ventricular fibrillation.\(^{22}\)

What are the relevance of these findings to clinical practice for the management of acute severe asthma? In a study of 257 adequately oxygenated patients who presented to the emergency department with acute severe asthma (FEV$_1$ <50\% predicted), cumulative doses of inhaled salbutamol (100 $\mu$g per puff) or fenoterol (200 $\mu$g per puff) were given as two puffs every 10 minutes up to a maximum cumulative dose of 16 puffs by means of a 145 ml Aerobchamber spacer.\(^{23}\) Prolongation of the QTc interval to a moderate degree (15–25\%) occurred in less than 5\% of patients and no patients showed marked (>25\%) prolongation. Thirty two patients exhibited one or more ventricular premature beats, but there were no episodes of sustained ventricular tachycardia or supraventricular tachycardia. Diastolic blood pressure, a surrogate for peripheral vasodilatation, showed mean decreases of 4.7 mm Hg and 2.4 mm Hg, respectively, in the fenoterol and salbutamol groups. In another study 178 patients with acute severe asthma (FEV$_1$ <50\% predicted) admitted to the emergency department were given either high dose nebulised salbutamol or intravenous salbutamol followed by intravenous aminophylline, although no mention was made of oxygenation status.\(^{24}\) Two hypotensive reactions were reported, both during the aminophylline infusions, but apart from this no significant systemic adverse effects were found in terms of either heart rate or blood pressure.

In summary, the potential for an interaction is only likely to be of relevance in the presence of severe uncorrected hypoxaemia with concomitant use of high doses of inhaled $\beta_2$ agonist. This reinforces the importance of adequately oxygenating patients with acute severe asthma receiving high doses of $\beta_2$ agonists, consistent with the conventional practice of nebulising with high flow oxygen. However, in the domiciliary setting where oxygen may not be available, the benefits of high dose $\beta_2$ agonist treatment will outweigh any theoretical risks of a potential interaction with hypoxaemia. The study by Burggraaf et al would suggest that it may be prudent for primary care doctors to co-administer nasal...
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